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Response to Final Office Action

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REMARKS

Claims 1, 28 and 40 have been amended to more particularly point out and distinctly claim the invention. Support for the amendments can be found throughout the specification. Claims 14 and 15 have been cancelled without prejudice or disclaimer.

Now pending are claims 1-13 and 16-53. No new matter has been added.

Amendment of any claim herein is not to be construed as acquiescence to any of the rejections/objections set forth in the instant Office Action, and was done solely to expedite prosecution of the application. Applicants make these amendments without prejudice to pursuing the original subject matter of this application in a later filed application claiming benefit of the instant application, including without prejudice to any determination of equivalents of the claimed subject matter.

Applicants submit that entry of the amendments is proper pursuant to 37 CFR 1.116 as the amendments merely cancel certain claims and put the remaining claims in better condition for allowance or appeal. Accordingly, entry and consideration of the amendments is proper and the same is requested.

Reconsideration of the application is requested.

Rejection under 35 USC §112, second paragraph

Claims 1-53 stand rejected under 35 USC §112, second paragraph, for allegedly lacking enablement. The Examiner states that "the specification, while being enabling for the disclosed compound . . . does not reasonably provide enablement for the variation in the R and Y groups as set forth in the independent claims." This rejection is traversed.

The Examiner states that Applicants have stated that "devising a compound that will exclusively bind to one of these ions is an unpredictable art." Applicants respectfully contend that this statement has been taken out of context: as pointed out in a previous response (dated September 20, 2005), the design of compounds that selectively bind to lithium would have been

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"unpredictable" to one of skill in the art *based on the state of the art at the time the invention was made*. However, enablement of the claims is evaluated in light not only of the knowledge of one of skill in the art at the time the invention was made, but also in view of the teachings of the present specification. "The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." MPEP 2164.08 (citation omitted). As described in the present specification, compounds according to the invention as claimed are selective for lithium ions; thus, the present disclosure, taken together with the knowledge of one of ordinary skill in the art at the time the invention was made, would have enabled the preparation and use of the compounds as claimed using no more than routine experimentation.

The Examiner also states that "the selectivity of the calixarene is dependent on the way in which the upper and or lower rims are functionalized." While Applicants agree that the selectivity of a calixarene can be affected by changing substituents at the upper or lower rims, the present specification provides guidance regarding the selection of appropriate functional groups. Thus, the present disclosure, taken together with the knowledge of one of ordinary skill in the art at the time the invention was made, would have enabled the preparation and use of the compounds as claimed using no more than routine experimentation. Accordingly, Applicants submit that the claims are enabled in their full scope, and withdrawal of this rejection is requested.

Moreover, while Applicants do not agree with the Examiner's position, to expedite prosecution, claims 1, 28 and 40, as amended, recite that R and Y are hydrogen (in the case of R) or alkyl. Applicants respectfully contend that functionalization with hydrogen and alkyl groups does not introduce "unpredictability" to one of ordinary skill in the art. A variety of compounds can be readily made and tested, e.g., as described in the present specification, without undue experimentation, and the claims are enabled in their full scope.

Even further, Applicants respectfully urge that this rejection cannot apply to claims 16-27; in these claims, the recited compounds do not include the variable groups R and X; and the group Y is not variable but rather has a fixed value (in these claims, Y is -CH₂-). In fact, claims

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16-27 are directed to compounds which feature identical functionality on the upper and lower rims of the calixarene moiety -- the same functionality, indeed, as the compound disclosed in Example 1 of the specification, which the Examiner has explicitly acknowledged is enabled. Claim 17 is directed to specifically to the compound disclosed in Example 1 of the specification, and therefore must be enabled (as the Examiner has admitted). Applicants therefore contend that the compounds according to claims 16-27 could readily be made and used by one ordinary skill in the art, based upon the teachings of the specification in view of the knowledge of one of ordinary skill in the art at the time the invention was made.

In the Office Action, the Examiner further states (at page 9) that "the scope of the claims appears to cover a large number of compounds . . . just within the R group a hydrogen, an alkyl amine, a carboxylic acid, a pyridinyl group a triazinyl group and a benzothiol group have different properties" As will be appreciated from the discussion above, this statement is largely inapplicable to the pending claims, in which the R moiety encompasses hydrogen and alkyl groups.

The Examiner then refers (at page 10 of the Office Action) to a publication, dated subsequent to the effective filing date of the present application, which discloses a compound as described in the present specification. The Examiner also states that "a search on the instant inventors did not yield any other publications after this describing a calixarene molecule for complexing lithium that is within the instant claim scope." Applicants respectfully point out that Applicants are not required to publish examples of the invention in order to enable their claimed invention. To denigrate the present invention by suggesting that "it would seem that applicant has not had any success yet" is improper.

Applicants respectfully contend that the specification provides enablement for the full scope of the pending claims, and, furthermore, that the claims meet all the requirements of, *inter alia*, 35 USC §112. Reconsideration and withdrawal of the rejection is requested.

Rejection under 35 USC §103(a)

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Claims 1-53 stand rejected under 35 USC §103(a) as being unpatentable over Benco or Kim in view of Pacey and Barnard. This rejection is traversed.

The Benco reference has been discussed in previous Responses. As discussed therein, the Benco reference is directed to a compound capable of selectively binding *potassium* ions. The Benco reference describes a calix[4]arene with an azacrown ether portion having four oxygen atoms and one nitrogen atom. As the Examiner appears to agree, the Benco reference does not teach or suggest azacrown calix[4]arenes sized to capture lithium ions. Applicants respectfully contend that the Benco reference, whether taken alone or in combination with the other cited references, does not render the claimed invention obvious.

The Kim reference, as it is understood by Applicants, describes studies of metal ion complexation by certain calixazacrown ethers. However, as the Examiner notes, the Kim reference "does not teach an azacrown calix[4]arene sized to capture lithium or structures related to sensor formation." Applicants respectfully contend that the Kim reference, whether taken alone or in combination with the other cited references, does not render the claimed invention obvious.

First, the Examiner points to the passage at page 2387, first full paragraph, as stating that "it is *possible* that the combination of N-chromogenic azacrown ether and calixcrown ether would result in an optimized structure for metal ion encapsulation." (emphasis supplied) Applicants respectfully submit that the passage cited by the Examiner follows a discussion of the complexation of *cesium* ion by certain calix[4]arenes; this discussion is silent as to whether these factors would be relevant to optimization of *lithium* complexation. Moreover, the passage cited by the Examiner refers to "possible" combinations which could result in optimized structure for metal ion complexation; this falls far short of teaching specific structural features for optimizing *lithium* ion complexation.

Second, the Examiner states that "[c]ompound 3-4 [of the Kim reference] are based on the structure of compounds 1-2," Office Action at page 6. However, Applicants point out that the Kim reference states that compound 1 (an aza-15-crown-5) shows lithium selectivity (p.2386,

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col. 2), whereas compound 3 (the calix[4]arene azacrown-5 compound) provides greater extractability for potassium and rubidium than for lithium (Table 1). Moreover, while compound 3 can transport lithium ion across a membrane in the absence of other metal ions (Table 2), compound 3 transports little or no lithium in the presence of potassium (Table 3). Therefore, the Kim reference demonstrates that the properties of azacrowns (such as compound 1) and the properties of structurally related calix[4]arene azacrowns (such as compound 3) may be substantially different, e.g., with respect to selectivity for metal cation complexation. Moreover, none of the calix[4]arenes of Kim is selective for lithium ion.

The Examiner states that the Pacey reference teaches chromogenic aza-12-crown-4 ethers for determination of lithium ions. However, as the Examiner concedes, the Pacey reference does not teach or suggest the preparation of calix[4]arene azacrown ethers, nor whether such compounds would have any selectivity for lithium. Applicants respectfully contend that the Pacey reference, whether taken alone or in combination with the other cited references, does not render the claimed invention obvious.

The Barnard reference is cited in the Office Action as teaching immobilized ionophores as optical metal ion sensors. The Examiner refers to general discussion in the Barnard reference in which calixarenes (but not calix[4]arene azacrown ethers) are mentioned; no compounds according to the presently-claimed invention are disclosed by Barnard. Barnard also does not provide any guidance which would teach or suggest the modification of the compounds disclosed in any of the other cited references so as to arrive at the compounds of the present invention. Applicants respectfully contend that the Barnard reference, whether taken alone or in combination with the other cited references, does not render the claimed invention obvious.

Despite the deficiencies of each of the cited references, the Examiner asserts that

[I]t would have been obvious to one of ordinary skill in the art . . . to modify the azacrown portion of the Benco or Kim fluoroionophore to correspond to that of the difference between the model azacrown of Benco or Kim and the similar azacrown of Pacey because of the recognition that the binding is related to the size fit and other types of effects and the teaching in Pacey that lithium is an important analyte that can be complexed by the smaller azacrown with a high

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selectivity with respect to the complexation of sodium and other alkali metals in a biological sample.

Office Action at page 8. This statement is traversed.

First, as discussed above, none of the cited references teaches the presently-claimed compounds, devices or methods. Indeed, while the Examiner appears to take the position that it would be possible to "modify the azacrown portion of the Benco or Kim fluoroionophore to correspond to . . . the similar azacrown of Pacey," such a suggested modification of the compounds of Benco or Kim *would not* result in the compounds of the present invention. The Examiner has pointed to Pacey as disclosing chromogenic aza-12-crown-4 ethers; however, the compounds of the present invention are not aza-12-crown-4 ethers. An aza-12-crown-4 ether (as disclosed in Pacey) has one nitrogen atom and three oxygen atoms in the azacrown ether ring. In contrast, the compounds of the present invention have only two oxygens in the azacrown ether portion of the calix[4]azacrown ether ring (differing also from Pacey in having a calixarene portion).

As pointed out by Applicants in a previous response, the Examiner's proposed combination of references does not take into account this difference in the structure of the presently-claimed compounds from any of the compounds of the cited references. None of the references provide any motivation to modify the compounds described in the references in this way. None of the references, whether taken alone or in combination, provide any indication that such a modification – even if possible, which is *also* not taught or suggested by the references – would result in compounds having useful selectivity for lithium ions. The references are simply silent on this point.

Even further, Applicants point out that the cited references do not teach or suggest the compound of claim 16 (and claims dependent therefrom). In claim 16, the calixarene moiety bears specific substituents – e.g., the t-butyl groups on the phenyl rings of the calixarene portion – which are not disclosed by any of the cited references, and therefore cannot be taught or suggested by those references, whether taken alone or in combination. Indeed, the Examiner

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refers (at page 12 of the Office Action) to "the differences between the structure of the compound claimed in claim 16 and the structure that examiner believes is suggested by the combination of references – the compound of claim 16 minus the t-butyl groups." Applicants respectfully contend that the Examiner has conceded – properly, in Applicants' view -- that the "combination of references" of record does not teach or suggest the compound of claimed 16 (and claims dependent therefrom). None of the cited references teaches or suggests a calixarene bearing a t-butyl substituent; no combination of the cited references can render obvious the invention of claim 16 (and claims dependent therefrom). Accordingly, Applicants urge that claims 16-27 are patentable over the cited references for at least these additional reasons.

Applicants contend that, prior to the present invention and absent the teachings of the present specification, one of ordinary skill in the art would not have been motivated to modify or combine the teachings of the cited references as suggested by the Examiner to arrive at the claimed invention. As the Court of Appeals for the Federal Circuit has stated, an Examiner "cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *See, e.g., In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1780, 1783 (Fed. Cir. 1988).

In the present case, the Examiner has chosen certain isolated features from a variety of references and attempted to combine them to arrive at the claimed invention by using the present disclosure as a blueprint. Applicants submit that a *prima facie* case of obviousness cannot be made in this instance. Thus, the cited references cannot render the claimed invention obvious, whether they are considered alone or in any combination.

In the Office Action (at page 11), the Examiner states (in response to Applicants' previous arguments) that

one of skill in the art would have expected that the calixarene azacrown ethers of Kim and Benco with smaller azacrown portions consistent with the size difference between the ring size of the Kim and Benco model compounds and the Pacey compound would have selectivity towards lithium based on at least the size aspect.

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Office Action at page 11. This statement is traversed; as discussed above, the compounds of the invention differ from every compound discussed by the Examiner in *all* of the cited references; the combination of references therefore cannot teach or suggest structural features not found in any of the references.

To the extent the Examiner appears to argue that it would have been obvious to one of skill in the art to try to modify the compounds of the references to arrive at the presently-claimed compounds, Applicants point out that "obvious to try" is not a proper rationale for an obviousness rejection. MPEP 2145(X)(B). Here, even if the Examiner's arguments were well-founded to some extent and the references provided the requisite suggestion to make *certain* modified compounds, the prior art references simply do not provide any motivation to make modifications which would result in the claimed compounds, nor any reasonable expectation that such modifications would be successful. As discussed above, none of the cited references teaches or suggest a calix[4]arene azacrown ether sized to selectively capture lithium, as the Examiner has conceded. Thus, the prior art references do not provide any suggestion or motivation to make the presently-claimed compounds. Without such suggestion or motivation, the rejection cannot stand.

The Examiner states (at page 12 of the Office Action) that "there is motivation to make the suggested change [in ring size] based on the difference in ring size between the azacrown ethers of Benco or Kim and Pacey". This statement is traversed. The Examiner appears to suggest that any modification of ring size would be obvious because Benco and/or Kim disclose that compounds having differing ring sizes may have different selectivities for ions. This cannot be correct: in order for the references (alone or in combination) to render obvious a claimed invention, the references must suggest the desirability of the claimed invention. See, e.g., MPEP 2143.01. As further provided by the MPEP, the fact that references *can* be combined or modified is not sufficient to establish *prima facie* obviousness (MPEP 2143.01(II)). As pointed out above, none of the references teaches or suggests that the *claimed compounds* would be selective for lithium ion. Thus, the references (whether taken alone or in combination) cannot render obvious the claimed invention.

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Finally, the statement that "it would have been obvious . . . to incorporate the fluoroionophore of Benco into a carrier material and or onto a support as taught by Barnard," Office Action at page 8, also misses the mark. Without some teaching or suggestion to make the compounds of the present invention, there could be no teaching or suggestion of the methods and devices of the present invention. Reconsideration and withdrawal of the rejection is proper and the same is requested.

The arguments discussed above also apply to the ground of rejection in which Pacey is used as a primary reference and Benco or Kim and Barnard are used as secondary references. As described above, modification of the compounds of Pacey, as suggested by the Examiner, simply would not result in the compounds of the present invention. Reconsideration and withdrawal of this new ground of rejection is also proper and the same is requested.

The Examiner has also once again stated (at page 12 of the Office Action) that "there is no limitation relative to the selectivity of the claimed compounds for lithium over sodium or potassium." This statement is not understood; as Applicants have previously pointed out, the present compound claims (claims 1 and 16 and claims dependent therefrom) clearly recite that the compound "selectively binds lithium ions as compared to potassium and/or sodium ions." Moreover, the remaining claims are specifically directed to devices "for the detection of lithium ions" or methods "for determining lithium ion concentration" of a fluid. Reconsideration is therefore respectfully requested.

Double Patenting Rejection

Claims 1-53 stand rejected under the judicially-created doctrine of obviousness-type double patenting "as being unpatentable over claims 1-28 of U.S. Patent No. 6,660,526 in view of Benco, Pacey and Barnard as explained above. This rejection is traversed.

As the MPEP makes clear, an obviousness-type double patenting rejection can only be maintained only if "any claim in the application [defines] an

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invention that is merely an obvious variation of an invention claimed in [an earlier patent]." MPEP 804(II)(B)(1). In the present case, the pending claims are not obvious variations of the claims of U.S. Patent No. 6,660,526 in view of the cited references for at least the reasons described above. Reconsideration and withdrawal of the rejection is proper and the same is requested.

CONCLUSION

Applicants believe that this application is in condition for allowance. Early and favorable action is requested.

The undersigned requests any extensions of time necessary for response. Although it is not believed that any additional fees are needed to consider this submission, the Director is hereby authorized to charge our Deposit Account No. 04-1105 should any fee be deemed necessary.

If the Examiner considers that obstacles to allowance still exist, the undersigned invites a telephone call at the number indicated below.

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Respectfully submitted,

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